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## Dopamine D<sub>2</sub> up-regulation in psychosis patients after antipsychotic drug treatment

*Ilse A. Thompson<sup>a</sup>, Erik F.J. de Vries<sup>b</sup>, and Iris E.C. Sommer<sup>c</sup>*

### Purpose of review

Recently, it has been questioned whether the re-emergence of psychotic symptoms following antipsychotic discontinuation or dose reduction is attributable to underlying psychotic vulnerability or to rebound effects of chronic use of antipsychotic medication. It was repeatedly shown that relapse rates are high after discontinuation of maintenance treatment. A potential contributing factor could be the increase in density of postsynaptic dopamine D<sub>2</sub> receptors in the striatum and the higher affinity of D<sub>2</sub> receptors for dopamine after chronic blockade.

## Recent findings

To date, little clinical evidence is available for the mechanisms involved in postsynaptic striatal D<sub>2</sub> receptor up-regulation after use of antipsychotic medication, and most knowledge comes from animal studies.

## Summary

Further research is needed to investigate whether antipsychotic medication causes neuroadaptations leading to a dopamine supersensitive state in humans, how long such hypersensitive states may last and what differences exist between high and low D<sub>2</sub> affinity antipsychotic drugs. Further, information is needed on discontinuation schedules that provide optimal protection for relapse during hypersensitive periods.

## Keywords

antipsychotic medication, dopamine D<sub>2</sub> up-regulation, dopamine supersensitivity psychosis, relapse

## INTRODUCTION

Schizophrenia spectrum disorders are clinically characterized by positive symptoms (e.g. hallucinations and delusions), negative symptoms (e.g. motivational impairment, social withdrawal and apathy) and cognitive alterations (e.g. an inability to sustain attention and poor executive functioning). Several theories have tried to explain the onset of psychotic symptoms, of which the dopaminergic theory is the most accredited one. This theory states that a complex dopaminergic dysregulation may underlie the positive symptoms of schizophrenia [1]. Pharmacotherapy with antipsychotic medication is the standard treatment for patients who experience psychosis, according to most national and international guidelines [2,3]. All antipsychotics act downstream at the dopamine D<sub>2</sub> receptors on the postsynaptic terminals to reduce dopamine-mediated signaling, which reduces psychotic symptoms. Chouinard *et al.* [4] proposed that chronic use of antipsychotic medication may lead to compensatory changes and a dopamine-sensitive state. Dopamine (super)sensitivity (DSP) is the excessive response to the (natural, or amphetamine-induced)

release of dopamine. DSP is characterized by the rapid re-emergence of psychotic symptoms after discontinuation or dose reduction of antipsychotic medication, and subsequent tolerance to antipsychotic treatment and eventually refractoriness [5]. A plausible explanation for (super)sensitivity to

<sup>a</sup>University of Groningen, University Medical Center Groningen, Department of Biomedical Sciences of Cells & Systems, Section of Cognitive Neurosciences, <sup>b</sup>University of Groningen, University Medical Center Groningen, Department of Biomedical Sciences of Cells & Systems, Section of Cognitive Neurosciences, Groningen and <sup>c</sup>University of Groningen, University Medical Center Groningen, Department of Biomedical Sciences of Cells & Systems, Section of Cognitive Neurosciences, Groningen, the Netherlands

Correspondence to Ilse A. Thompson, MSc, University of Groningen, University Medical Center Groningen, Department of Biomedical Sciences of Cells & Systems, Cognitive Neurosciences, Groningen, the Netherlands. E-mail: i.a.thompson@umcg.nl

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## KEY POINTS

- There is no clear evidence for a relationship between dopamine D<sub>2</sub> receptor up-regulation and dopamine supersensitivity psychosis (DSP) in schizophrenia patients;
- Risk for relapse of psychosis is high, which may be increased with prolonged exposure to antipsychotics;
- The potential mechanism behind high relapse rates, in patients who discontinue antipsychotic medication after maintenance treatment, may be D<sub>2</sub> receptor up-regulation;
- Further research is needed to determine whether changes in dopamine neurotransmission are present in patients after starting antipsychotic treatment.

dopamine is the up-regulation of D<sub>2</sub> receptor expression or an increase in the fraction of the receptors that are in the high-affinity state [4]. In the time the hypothesis was put forward, antipsychotic dosing regimen tended to be a 10–20-fold higher than now. However, this up-regulation may cause a potentially supersensitive postsynaptic receptor system, which, in combination with a presynaptic dopaminergic system not being sufficiently suppressed, may increase the risk of relapse after discontinuation. Previous studies have indicated that the risk of symptom recurrence was between 67 and 77% one year after discontinuation, and had increased to over 90% two years after discontinuation [6<sup>•</sup>,7]. Interestingly, the former study [6<sup>•</sup>] also investigated whether the length of antipsychotic treatment before discontinuation associated with risk of relapse. The groups were divided into 12 months or less of antipsychotic treatment ( $n = 42$ ), and at least 12 months treatment ( $n = 20$ ). Interestingly, it was noted that the duration of prior antipsychotic treatment was not associated with a reduced risk of relapse. However, other studies show an increase risk of relapsing when discontinuing, as studies show that patients who do not use antipsychotic medication for a prolonged time are significantly less likely to relapse [8,9]. These figures clearly issue a warning against discontinuation of maintenance therapy, as risk for recurrence of psychosis is high, but they also indicate that recurrence rates become even higher with prolonged exposure to antipsychotics when discontinuing treatment. Thus, while it is widely assumed that a psychotic episode following antipsychotic discontinuation or dose reduction is attributable to the underlying psychotic illness, there have been concerns that discontinuation after maintenance treatment may actually make patients

more vulnerable to psychotic relapse than would be the case in the natural course of the illness without antipsychotic treatment [10]. It is important to emphasize that the validity of the DSP hypothesis, namely an up-regulation of dopamine D<sub>2</sub> receptors provoked by chronic and long-term occupancy of dopamine D<sub>2</sub> receptors, leading to an increased density of postsynaptic dopamine D<sub>2</sub> receptors in the striatum, has not been fully proven yet, at least not in clinical studies [11]. In this review, we will summarize the evidence for and against this hypothesis.

## ANIMAL STUDIES

A possible mechanism underlying DSP may be an increased dopamine D<sub>2</sub> receptor density in the striatum. Several studies have shown that the chronic administration of haloperidol indeed increased the dopamine D<sub>2</sub> receptor density in the striatum in rodents [12<sup>••</sup>,13–16]. The most recent study [12<sup>••</sup>] evaluated the effects of 21-day repeated administration of haloperidol at 1 mg/kg and brexpiprazole at 4 mg/kg on striatal dopamine D<sub>2</sub> receptor density in rats, and found that while haloperidol increased the density, brexpiprazole showed no effect, compared to vehicle treatment. This suggests that brexpiprazole may have a lower risk of increasing the D<sub>2</sub> receptor density, and possible consequently relapsing after repeated administration. A recent study indeed shows fewer relapses in brexpiprazole compared to cariprazine and lurasidone [17]. Another recent study [13] compared blonanserin at 0.78 mg/kg with haloperidol at 1.1 mg/kg twice daily for 28 days. The results showed an increased striatal dopamine D<sub>2</sub> receptor density in the rats treated with haloperidol, whereas blonanserin did not show an effect. This suggests that blonanserin is less likely to induce an up-regulation of the dopamine D<sub>2</sub> receptor density as compared to haloperidol. Furthermore, aripiprazole at 10 mg/kg has been shown to cause up-regulation of the dopamine D<sub>2</sub> receptor [18], although another study with a lower dose of 1.5 mg/kg did not show an up-regulation of the D<sub>2</sub> receptors [16]. Olanzapine at 10 mg/kg has also been shown to not increase the D<sub>2</sub> receptors [15].

Moreover, the study by Amada *et al.* [12<sup>••</sup>] reported that the chronic treatment of risperidone (1.5 mg/kg) significantly increased locomotor activity induced by apomorphine (0.1 mg/kg;  $P < 0.01$ ), suggesting sensitized D<sub>2</sub> receptors in rats after the chronic treatment of risperidone. The study by Hashimoto *et al.* [13] reported significantly enhanced hyperlocomotion in rats treated with haloperidol, whereas with blonanserin, the total hyperlocomotion was not significantly different to vehicle-treated rats. This suggests that blonanserin might be less

likely to induce DSP after chronic administration, compared to haloperidol.

Another possible mechanism to underlie DSP is the increase in number of dopamine  $D_2^{\text{high}}$  receptors. It is known that dopamine  $D_2$  receptors can exist in a state of high-affinity (G-protein-coupled high-affinity;  $D_2^{\text{high}}$ ) or in a state of low-affinity for dopamine (G-protein-uncoupled low-affinity;  $D_2^{\text{low}}$ ) [19]. Dopamine  $D_2^{\text{high}}$  is the functionally active state of the dopamine  $D_2$  receptor [19]. While antipsychotic medication may not elevate the density of dopamine  $D_2$  receptors, it has been shown that they can increase the number of dopamine  $D_2^{\text{high}}$  receptors in animal studies [20]. Although it should be noted that the animals in this study were still being treated with olanzapine when the analysis was performed, with an occupancy of approximately 70%. The study by Samaha *et al.* [21] investigated presynaptic and postsynaptic elements of the dopaminergic system during ongoing treatment by measuring the ability of haloperidol to inhibit amphetamine locomotion. They found a tolerance to increase dopamine and dopamine turnover presynaptically, while showing a 20–40% increase in  $D_2$  receptor number postsynaptically, and 100–160% increases in the proportion of  $D_2^{\text{high}}$  postsynaptically. These results suggest that antipsychotic treatment may lose its efficacy related to dopamine  $D_2$  receptor increase.

Another study [22] investigated whether continuous or intermittent treatment induced amphetamine-induced locomotion in rats, as an indication of antipsychotic-induced dopamine supersensitivity. Haloperidol was continuously or intermittently administered for 16–17 days. After 3–5 days, amphetamine-induced locomotion was measured. The results showed that only the rats with continuous treatment showed enhanced amphetamine-induced locomotion. It could be argued that continuous treatment with antipsychotic drugs may cause neuroadaptations, inducing supersensitive behavior, whereas intermittent dosing is not associated with such behavior [22,23]. This could be of clinical interest, as present patient guidelines recommend 1-year continuous antipsychotic treatment after an episode of psychosis. It could be argued that some patients benefit from continuous treatment, whereas it might also promote neuroadaptations that could cause dopamine supersensitivity. However, relapse rates are shown to be high after 1–2 years of treatment who are treated with depot antipsychotics (i.e. continuous treatment with high adherence).

## CLINICAL STUDIES

Whereas animal studies have shown that chronic administration of antipsychotic treatment can lead

to neuroadaptations, there are very few recent clinical studies examining whether antipsychotic medication plays a role in the up-regulation of dopamine  $D_2$  receptors in humans, and whether relapse following antipsychotic withdrawal is linked to an up-regulation of dopamine  $D_2$  receptors. Clear evidence that chronic exposure of antipsychotic medication can lead to a ‘dopamine supersensitive state’ is lacking [24].

### Clinical studies investigating the role of antipsychotic medication in neuroadaptations

The first clinical study [25] investigating the role of antipsychotic medication in the up-regulation of dopamine  $D_2$  receptors compared patients with schizophrenia ( $n=9$ ) who had received long-term antipsychotic treatment relative to antipsychotic-naïve patients with schizophrenia ( $n=8$ ). Patients were treated with first-generation antipsychotics (e.g. haloperidol, perphenazine) and second-generation antipsychotics (risperidone, olanzapine) in moderate to high dosages. Fourteen days after drug withdrawal, the binding potentials of dopamine  $D_2$  receptors were measured using positron emission tomography (PET) using [ $^{11}\text{C}$ ]raclopride, a radioligand of the dopamine  $D_{2/3}$  receptor antagonist. Results showed that long-term treatment with antipsychotics were associated with a substantial increase of 30% in  $D_2$  receptor binding in the striatum. Another study [26] scanned eight antipsychotic-naïve patients with schizophrenia, using [ $^{11}\text{C}$ ](+)-PHNO PET – a radioligand of the dopamine  $D_{2/3}$  receptor antagonist, to estimate dopamine  $D_{2/3}$  receptor binding in patients. Patients were scanned before treatment and after approximately 2.5 weeks of treatment of either olanzapine at 10 mg/day or risperidone at 2–3 mg/day. Results show that 40–45% of the  $D_{2/3}$  receptors in the caudate and putamen was occupied by the therapeutic drug (i.e. less receptor availability). The authors suggest that this lower receptor availability might be due to lower doses used in first episode patients. Indeed, a small but significant elevation in  $D_{2/3}$  receptor availability has been found in patients who use antipsychotic medication ( $d=0.26$ ,  $P=0.049$ ) as compared to antipsychotic-naïve patients, although this finding is not consistent across studies [27]. Moreover, when caudate and putamen in treated patients were analyzed separately, no significant differences in  $D_{2/3}$  receptor availability were observed. Interestingly, the results of the meta-analysis show that dopamine  $D_2$  receptor density is unaltered in drug-naïve patients before antipsychotic medication, which suggests that  $D_2/D_3$  alterations are not intrinsic to the illness,



but may be secondary to chronic antipsychotic treatment [27]. It has been suggested that 36–39% of relapsed patients chronically treated with antipsychotic medication show dyskinesia, suggesting that these patients may be ‘supersensitive’ [28,29]. However, it should be noted that this study associated abnormal involuntary movements (i.e. dyskinesia) with D<sub>2</sub> hypersensitivity, but did not measure dopamine D<sub>2</sub> receptor availability. Contradictory to those results are the results of another study [30] that found no differences between patients discontinued after treatment with either placebo ( $n=97$ ) or ongoing antipsychotic treatment ( $n=36$ ) (paliperidone palmitate once monthly). This clinical study was conducted to compare the nature of relapse after either condition, in terms of onset and severity of psychotic symptoms, the presence of tardive dyskinesia and the relapse symptom profiles. Thus, the authors state that the study found no evidence for withdrawal-related phenomena contributing to high relapse rates after the discontinuation of antipsychotic medication.

### **Clinical studies investigating possible biomarkers for the development of dopamine supersensitivity psychosis**

In a recent study [31<sup>•</sup>], first episode psychosis patients ( $n=25$ ) were compared to healthy controls ( $n=14$ ) to investigate whether dopaminergic function changes after the discontinuation of antipsychotic medication. At baseline patients started tapering off medication, and at 4 weeks patients completed tapering off. The participants completed two [18F]FDOPA PET scans: at baseline (i.e. prediscontinuation) and after 6 weeks of treatment (i.e. 2 weeks postdiscontinuation), and a [11C]raclopride PET scan at 7 weeks. The results showed no significant difference between relapsed and nonrelapsed patients in dopamine D<sub>2</sub> availability, although a trend towards significance was observed ( $P=0.055$ ). Furthermore, relapsing patients showed an increase in dopamine synthesis, compared to nonrelapsing patients. This is in line with previous research, suggesting that relapse may be associated with presynaptic abnormalities instead of with postsynaptic D<sub>2</sub> availability or dopamine transporters [27]. The authors suggest that relapsed patients could be different in the underlying pathophysiology [31<sup>•</sup>]. Therefore, dopamine synthesis measured using PET could possibly be used for the prediction of relapse after discontinuing antipsychotic medication in a first episode of psychosis, by validating dopamine synthesis as a possible biomarker. Another recent study by Kanahara *et al.* [32] investigated the possible biomarker CYP2D6 – one of

the most important drug-metabolizing enzyme, which is suggested to be involved in dopamine supersensitivity. CYP2D6 may be a possible biomarker, as patients with an impaired allele may have higher concentrations of the antipsychotic and its active metabolite. Thirty-six patients were divided in two groups: one with normal metabolizing activity and the other with lower activity of its variant. The concentrations of risperidone and 9-OH-risperidone were measured in blood samples. The results showed that no effect of the enzyme, or metabolism on relapse could be detected. DSP may be associated with D<sub>2</sub><sup>high</sup>, but not with the total D<sub>2</sub> receptor density, as an increase in D<sub>2</sub><sup>high</sup> receptors without significant increases in dopamine D<sub>2</sub> receptors have been observed in an animal model by Seeman [33]. A recent study by Kubota *et al.* [34] indicated a higher proportion of D<sub>2</sub><sup>high</sup> in the putamen of drug-naïve ( $n=10$ )/drug-free ( $n=1$ ) patients with schizophrenia as compared to healthy controls, despite the total amount of dopamine D<sub>2</sub> receptors being unaltered. This is in line with Chouinard *et al.* [35], who proposed that the chronic use of antipsychotics may increase the total number of dopamine D<sub>2</sub> receptors and dopamine D<sub>2</sub><sup>high</sup> receptors in the striatum, without showing significant changes in the presynaptic dopamine release, synthesis, or reuptake. The authors hypothesized that the increase in D<sub>2</sub> receptors enhances D<sub>2</sub>-mediated dopamine signaling, which produces a state of supersensitivity to stimulation of a dopamine agonist. This could lead to DSP. However, it is not clear whether this effect is caused by antipsychotic treatment, as the studies by Kubota *et al.* [34] and Seeman [33] found, enhanced high-affinity D<sub>2</sub> receptor density in patient and animal models without antipsychotic treatment. To date, only a limited number of studies investigated whether alterations exist in the amount of D<sub>2</sub><sup>high</sup> or in the proportion of D<sub>2</sub><sup>high</sup> ligand binding in patients with schizophrenia [34], and there is no evidence yet about the effect of drug discontinuation on the affinity state of D<sub>2</sub> receptors. High relapse rates have been associated with antipsychotic treatment resistance [36<sup>••</sup>], as it has been shown that antipsychotic dose is significantly higher in patients after a second episode of psychosis [36<sup>••</sup>]. However, it could be argued that this may actually be the up-regulation of dopamine D<sub>2</sub> receptors, as the animal model by Samaha *et al.* [21] demonstrated a reduced efficacy after long-term administration of antipsychotic medication, which could be partly compensated by an increase in drug dose. Furthermore, the studies showed that both the concentration of D<sub>2</sub> receptors and the fraction of receptors in the high-affinity state were significantly increased when resistance occurred.

## CONCLUSION

While it is widely assumed that the re-emergence of psychotic symptoms following antipsychotic discontinuation (or reduction) is attributable to the underlying psychotic vulnerability, relapse risk may partly be caused by receptor up-regulation after chronic antipsychotic use. There is sparse clinical evidence for dopamine supersensitivity, but stronger evidence from animal studies. Antipsychotic drugs with lower D<sub>2</sub> blockade, such as the partial agonist aripiprazole, lower dose and intermittent treatment, seem to reduce this risk [16]. Thus, maintenance therapy at the lowest possible dose is needed to obtain clinical stability, as risk for symptom recurrence after withdrawal is very high. When patients want to discontinue antipsychotic medication, tapering off should be performed over prolonged time (3–6 months) and under regular supervision. A previous study showed that in FEP patients this was feasible in only 20% [37]. Because antipsychotic medication is the mainstay of treatment in psychosis, a greater understanding of dopamine up-regulation and its prevention may greatly affect patient outcomes. To date, little clinical evidence is available for the mechanisms involved in postsynaptic striatal D<sub>2</sub> receptor up-regulation and the influence of antipsychotic medication. Therefore, new clinical studies are needed to investigate whether changes in dopamine neurotransmission are present in (drug-naïve) patients after starting antipsychotic treatment.

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## Conflicts of interest

There are no conflicts of interest.

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- of special interest
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